BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the Matter of the Application of: Gelfer et al.

Serial No.: 08/300,510

Filed: September 2, 1994

For: COMPOSITIONS AND METHODS FOR ADMINISTERING TO HUMANS, PEPTIDES CAPABLE OF DOWN REGULATING AN ANTIGEN SPECIFIC IMMUNE RESPONSE

Attorney Docket No: IMI-045

Group Art Unit: 1644

Examiner: Cunningham, T. M.

#36
AGJ
11/3/98

Assistant Commissioner for Patents
Box AF
Washington, D.C. 20231

CERTIFICATE OF FIRST CLASS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Box AF, Washington, D.C. 20231 on the date set forth below.

October 26, 1998
Date of Signature
and Mail Deposit

By Jeanne M. DiGiorgio
Jeanne M. DiGiorgio
Reg. No. 41,710
Attorney for Appellants

APPEAL BRIEF

This Appeal Brief is responsive to the Defective Notice of Appeal or Brief dated September 24, 1998. Please substitute this Appeal Brief for Appeallants' prior Appeal Brief submitted on July 17, 1998. Accordingly, this brief is submitted in triplicate. A Fourth Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 is being filed on even date herewith.

As set forth in the notice of appeal received by the Patent Office on June 12, 1997, Appellants hereby appeal the final decision of the Examiner rejecting the pending claims of the above-identified application.

A check in the amount of $155.00 for the Appeal Brief Fee as set forth in 37 C.F.R. §1.17(f) was sent on December 12, 1997. No other fees are believed to be due in connection with the filing of this Appeal Brief.

Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the Examiner's rejection of all the claims.

I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Immulogic Pharmaceutical Corporation.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellants, Appellants' legal representative or the assignees which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 108, 109, 114-117, 120-123, and 128-144 are pending in this application. Claims 103-107, 110-113, 118,119, and 124-127 have been canceled and claims 114, 115, 120-122, 128, 130, 131, 133, 134, and 136-138 have been amended as described in the Fourth Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116, which is being filed on even date herewith. The amendment and/or cancellation of these claims reduces the number of issues for appeal. It is assumed that the Amendment and Response to Final Office Action will be entered for purpose of appeal and the claims argued herein will reflect this assumption. All of the pending claims, 108, 109, 114-117, 120-123, and 128-144, are on appeal and are set forth in Appendix A of this Brief.

IV. STATUS OF THE AMENDMENTS

A Fourth Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 is being filed on even date herewith in response to the final Office Action dated December 10, 1996. At the time the Amendment was filed, claims 103-144 were pending in the application. A Notice of Appeal was filed separately on June 10, 1997 and received by the U.S. Patent Office on June 12, 1997.

In the Fourth Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116, claims 103-107, 110-113, 118,119, and 124-127 have been canceled and claims 114, 115, 120-122, 128, 130, 131, 133, 134, and 136-138 have been amended.

The amendment of claim 114, 115, 120-122, 128, 130, 131, 133, 134, and 136-138 corrects improper dependency. The amendment of claim 133 obviates the rejection of claim 133 under 35 U.S.C. §112, second paragraph and claims 108-109 as they encompass the use of nonimmunogenic peptides under 35 U.S.C. §112, first paragraph. Accordingly, the amendment of claim 133 reduces the number of issues for appeal.

It is assumed that the Fourth Amendment and Response to Final Office Action will be entered for purpose of appeal and the claims argued herein will reflect this assumption.

An Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 was filed on June 10, 1997 in response to the final office action dated December 10, 1996 and was not entered. A Notice of Appeal was filed separately on June 10, 1997 and received by the U.S. Patent Office on June 12, 1997.

A Second Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 was filed on December 12, 1997 in response to the final office action dated June 10, 1997 and was not entered.

A Third Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 was filed on April 6, 1998 in response to the Advisory Action dated March 5, 1998 and was not entered.

A Fourth Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 is being filed on even date herewith.

Claims 108, 109, 114-117, 120-123, and 128-144 are pending in this application. Claims 114, 115, 120-122, 128, 130, 131, 133, 134, and 136-138 have been amended as described in the Fourth Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116, which is being filed on even date herewith. The amendment and/or cancellation of these claims reduces the number of issues for appeal. It is assumed that the Amendment and Response to Final Office Action will be entered for purpose of appeal and the claims argued herein will reflect this assumption. All of the pending claims, 108, 109, 114-117, 120-123, and 128-144, are on appeal and are set forth in Appendix A of this Brief.

V. SUMMARY OF THE INVENTION

Appellants' invention pertains to methods for treating allergy in humans by administering at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response, e.g., a specific immune response to the elected species, *Fel d*I allergen, in the human wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, the peptide comprising at least about 20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen, and the peptide being reproducible and not cnjugated to any other molecule.

The methods for down regulation of an antigen specific response by administering at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response, e.g., a specific immune response to the elected species, *Fel d*I allergen, in the human are described in the present application at least at page 7, lines 7-26. Therapeutic compositions comprising at least one peptide having a defined sequence of amino acid residues comprising at least 20% of the T cell epitopes

recognized by T cell receptors specific for the protein allergen are described in the present application at least at page 8, lines 16-34, and at page 8, line 35 through page 9, line 15. Methods for synthesizing such peptides as well as peptides which are reproducible and not conjugated to any other molecule are described in the present application art least at page 14, lines 8-30, ant at page 15, lines 8-19.

VI. STATEMENT OF ISSUES PRESENTED FOR REVIEW

Appellants present the following issues for review:

I. Whether claim 133 is indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention as required under 35 U.S.C. § 112, second paragraph.

II. Whether claims 133 and 108-109 as they encompass the use of nonimmunogenic peptides contain subject matter which is not described in the specification in such a way to enable one skilled in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention as required under 35 U.S.C. § 112, first paragraph.

III. Whether the methods encompassed by claims 108, 109, 114-117, 120-123, and 128-144 are unpatentable as being obvious in view of the teachings of Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991).

VII. GROUPING OF CLAIMS

Claims 108, 109, 114-117, 120-123, and 128-144 are Appellants' principal claims on appeal. Claim 108 is an independent claim drawn to a method of treating allergy in

humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide comprising at least about 20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen, said peptide being reprodicuble and not being conjugated to any other molecule.

Claims 109, 114, 115, 120-122, 128, 130, 131, 133, 134, and 136-138 depend from the above described independent claim.

Claim 109 is directed to a peptide comprising 50 amino acid residues or less.

Claim 114 is directed to a peptide modified by at least one amino acid substitution, addition or deletion, said peptide comprising a T cell epitope recognized by a T cell receptor specific for the protein allergen.

Claim 115 is directed to a peptide purified to at least about 90% purity. Claim 116, which depends from claim 115, is directed to a peptide purified to at least about 95% purity. Claim 117, which depends from claim 116, is directed to a peptide purified to at least about 97% purity.

Claims 120-122 depend from any one of claims 108-109. Claim 120 is directed to a peptide at least about 12 amino acid residues in length. Claim 121 is directed to at least one peptide comprising at least two peptides. Claim 122 is directed to a protein allergen selected from the group consisting of: a protein allergen of the genus *Dermatophagoides*; a protein allergen of the genus *Felis*; a protein allergen of the genus *Ambrosia*; a protein allergen of the genus *Lolium*; a protein allergen of the genus *Cryptomeria*; a protein allergen of the genus *Alternaria*; a protein allergen of the genus *Alder*; a protein allergen of the genus *Betula*; a protein allergen of the genus *Quercus*; a protein allergen of the genus *Olea*; a protein allergen of the genus *Artemisia*; a protein allergen of the genus

Plantago; a protein allergen of the genus *Parietaria*; a protein allergen of the genus *Canine*; a protein allergen of the genus *Blattella*; a protein allergen of the genus *Apis*; a protein allergen of the genus *Cupressus*; a protein allergen of the genus *Juniperus*; a protein allergen of the genus *Thuya*; a protein allergen of the genus *Chamaecyparis*; a protein allergen of the genus *Periplaneta*; a protein allergen of the genus *Agropyron*; a protein allergen of the genus *Secale*; a protein allergen of the genus *Triticum*; a protein allergen of the genus *Dactylis*; a protein allergen of the genus *Festuca*; a protein allergen of the genus *Poa*; a protein allergen of the genus *Avena*; a protein allergen of the genus *Holcus*; a protein allergen of the genus *Anthoxanthum*; a protein allergen of the genus *Arrhenatherum*; a protein allergen of the genus *Agrostis*; a protein allergen of the genus *Phleum*; a protein allergen of the genus *Phalaris*; a protein allergen of the genus *Paspalum*; and a protein allergen of the genus *Sorghum*.

Claim 123, which depends from claim 122, is directed to the protein allergen selected from the group consisting of: *Der p* I; *Der p* II; *Der p* III; *Der p* VII; *Der f* I; *Der f* II; *Der f* III; *Der f* VII; *Fel d* I; *Amb a* I.1; *Amb a* I.2; *Amb a* I.3; *Amb a* I.4; *Amb a* I; *Lol p* I; *Lol p* II; *Lol p* III; *Lol p* IV; *Lol p IX* (*Lol p* V or *Lol p* Ib); *Cry j* I; *Cry j* II; *Can f* I; *Can f* II; *Jun s* I; *Jun v* I; *Dac g* I; *Poa p* I; *Phl p* I; and *Sor h* I.

Claim 128, which depends from any one of claims 108-109, is directed to a composition further comprising a pharmaceutically acceptable carrier.

Claim 129, which depends from claim 128, is directed to a pharmaceutically acceptable carrier comprising at least one excipient selected from the group consisting of sterile water, sodium phosphate, mannitol, sorbitol, sodium chloride, and any combination thereof.

Claim 130, which depends from any one of claims 108-109, is directed to a composition soluble in an aqueous solution at a physiologically acceptable pH.

Claim 131, which depends from any one of claims 108-109, is directed to routes of administration selected from the group consisting of oral, intravenous, sublingual, transdermal, inhalation, subcutaneous and rectal.

Claim 132, which depends from claim 131, is directed to subcutaneous administration of said composition.

Claims 133-134 depend from any one of claims 108-109. Claim 133 is directed to administration in non-immunogenic form. Claim 134 is directed to administering an initial treatment of three to six dosages of said composition over a period of no more than 6 weeks.

Claim 135, which depends from claim 134, is directed to administering an additional administration of said composition at intervals of between about three months and one year after said initial treatment.

Claims 136-138 depend from any one of claims 108-109. Claim 136 is directed to initial treatment comprising increasing the dosage with each subsequent additional dosage of said composition. Claim 137 is directed to initial treatment comprising decreasing the dosage with each subsequent additional dosage of said composition. Claim 138 is directed to treatment resulting in a statistically significant improvement in symptoms caused by the human's immune response to the protein allergen.

Claims 139-141 depend from claim 128. Claim 139 is directed to treatment resulting in at least about 17.5% improvement, as compared to placebo, in symptoms caused by the human's immune response to the protein allergen. Claim 140 is directed to treatment resulting in at least about 9% improvement, as compared to placebo, in nasal symptoms caused by the human's immune response to the protein allergen. Claim 141 is directed to treatment resulting in at least about 17.5% improvement, as compared to placebo, in lung symptoms caused by the human's immune response to the protein allergen.

Claims 142-144 depend from claim 139. Claim 142 is directed to treatment resulting in at least about 23% improvement. Claim 143 is directed to treatment resulting in at least about 31% improvement. Claim 144 is directed to treatment resulting in at least about 28.5 % improvement.

The rejected claims do not stand or fall together for the reasons set forth below.

VIII. ARGUMENTS

A. Rejection of Claim 133 Under 35 U.S.C. § 112, second paragraph

Claim 133 was rejected under 35 U.S.C. § 112, second paragraph, for being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention. Specifically, the Examiner states that "[i]n claim 133 it is unclear what the metes and bounds of the term 'nonimmunogenic' are."

Appellants respectfully submit that the phrase "nonimmunogenic form" is described in the subject specification and is art recognized terminology. Claim 133 requires administration of peptides in "non-immunogenic ***form***." The meaning of the term "in non-immunogenic ***form***" is not only described in clear detail in Applicants' disclosure, but was also art-recognized at the time of the invention and therefore would have been clear to one of ordinary skill in the art. Evidence of such can be found in numerous references published prior to the filing date of the present application, such as Kearney et al. (1994) *Immunity* 1:327-339, and Briner et al. (1993) *PNAS* 90: 7608-7613 discussed below.

As disclosed at page 7, lines 7-18, of the specification, stimulation of T cells requires two signals. The first signal is recognition of antigen presenting cells (APCs) by the T-cell receptor (TCR). The second signal is costimulation of T cells by a costimulatory or "second" signal produced by APCs in response to certain auxiliary stimuli, such as adjuvant. Without the occurrence of both T cell epitope recognition and costimulation by APCs, T cells are not stimulated and the various immune responses

which normally ensue are not induced. This is believed to be due to the fact that, in the absence of an agent such as adjuvant which causes APCs to produce the second signal or costimulatory signal, competent APC's are not engaged in the stimulation of appropriate T cells. This can then result in T cell non-responsiveness or reduced T cell responsiveness.

Thus, Appellants disclosure makes it clear that the term "in non-immunogenic form" means in a form which does not include an agent, such as an adjuvant, which induces the co-stimulatory properties of APCs (see, e.g., page 6, line 27 and page 7, line 15 of the specification).

The meaning of the term "in non-immunogenic form" was also discussed extensively in the literature at the time the present application was filed. For example, Kearney et al. (1994) *Immunity* 1: 327-339 teach that "monomeric antigen ***is only immunogenic if injected locally in an adjuvant***" (see page 327) (emphasis added) based on the need for co-stimulation of T cells by APCs. The authors teach that adjuvant "induces local inflammation which enhances the adhesive and costimulatory properties of APC's" (see page 327).

The meaning of administration "in non-immunogenic form" is similarly discussed by Briner et al. (1993) *PNAS* 90: 7608-7613. Specifically, the authors state that "*in-vivo* tolerance to antigen challenge has been shown using . . . peptides administered in such a way as to preclude the second signal [i.e., co-stimulation by APCs]" (see page 7608). Thus, the art came to know this mode of administration as administration ***in non-immunogenic form***.

Overall, both Appellants' disclosure and the literature at the time of the present invention would have made the metes and bounds of the term "in non-immunogenic form" clear to one of ordinary skill in the art. Accordingly, claim 133 is definite as required under 35 U.S.C. §112, second paragraph.

B. Rejection of Claims 133 and 108, 109, 114-117, 120-123, and 128-144 Under 35 U.S.C. § 112, first paragraph

Claims 133 and 108, 109, 114-117, 120-123, and 128-144 as they encompass the use of nonimmunogenic peptides were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner states that "[t]he peptides in the claimed methods are 'immunogenic' as they induce immune responses in human patients, see e.g. page 23, line 26 of the specification."

As described above, Appellants submit that the phrase "in non-immunogenic form" is art-recognized and an example of a "non-immunogenic" form described in the present specification is a form "not containing adjuvant" (see e.g., page 6, line 27, and page 7, line 15 of the specification). Thus, Appellants assert that claim 133 and 108, 109, 114-117, 120-123, and 128-144 contain subject matter which is described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

In addition, the statement by the Examiner that "***the peptides used in the claimed methods are immunogenic as they induce immune responses in human patients***" (emphasis added) is not entirely correct. T cell epitope containing peptides encompassed by the present claims are ***not*** immunogenic (as defined by T cell stimulation and the occurrence of various ensuing immune reactions such as recruitment of other immune cells, immunglobulins etc.) unless an agent - most commonly adjuvant - is administered along with the peptides to induce the co-stimulatory action of APCs required to cause T cell stimulation.

Therefore, based on the above-described teachings of Appellants that T cell epitope containing peptides can be administered in non-immunogenic form ***simply by not including an agent which induces the co-stimulatory action of APCs***, Appellants respectfully submit that the subject matter of claims 133 and 108, 109, 114-117, 120-123,

and 128-144 are fully enabled. Indeed, Appellants' disclosure teaches the most common manner of administering peptides in non-immunogenic, namely by simply omitting any adjuvant (see e.g., page 6, line 27, and page 7, line 15 of the specification). Thus, the disclosure would have fully enabled one of ordinary skill in the art to have made and used (e.g., administered) the peptides encompassed by claims 133 and 108, 109, 114-117, 120-123, and 128-144 without undue experimentation. Appellants accordingly respectfully request that the rejection be withdrawn.

C. Rejection of Claims 108, 109, 114-117, 120-123, and 128-144 Under 35 U.S.C. § 103 as Being Obvious in Light of Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991)

The present claims are drawn to a method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, the peptide comprising at least about 20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen, e.g., *Fel d*I, and the peptide being reproducible and not being conjugated to any other molecule. Thus, the compositions encompassed by the present claims provide the distinct advantage of being highly reactive, pure and reproducible, making them more effective, safer and eminently more suitable for human administration than compositions containing whole or partially digested native allergens obtained from crude allergen extracts.

Sehon et al. teach that conjugation of PEG to peptides can render peptides nonimmunogenic or "tolerogenic." For example, Sehon et al, teach "that the PEG conjugates did not induce anaphylatic death of animals and . . . therefore . . . appear to have the desirable properties of safe immunotherapeutic agents." Thus, the teachings of

Sehon et al. would ***not*** have suggested the use of ***unconjugated*** peptides in therapeutic compositions, as claimed by Appellants. In fact, the authors teach directly ***away*** from the use of unconjugated peptides in compositions for human therapy, since they disclose that modification, such as PEG conjugation, is necessary to render the peptides tolerogenic and safe. Moreover, as previously pointed out by Appellants, the Examiner agreed during the personal interview that Sehon et al. ***does not teach or suggest the use of a peptide per se or a therapeutic composition containing a peptide***.

Michael et al. also fail to provide any teaching or suggestion which would have led one of ordinary skill in the art to the claimed invention. Michael et al. teach proteolytic digestion of primary pollen allergens to produce pollen specific polypeptides. Proteolytic digestion of native allergen generates an ***irreproducible*** milieu of polypeptide fragments which have an ***unknown variable composition*** following each digestion. Moreover, not all of the proteolytically digested peptides are certain to contain a T cell epitope. Nor are the peptides highly pure since they are present along with a variety of other contaminating proteins with which the allergen naturally occurs.

In contrast, Appellants claim therapeutic compositions made up of a ***reproducible*** selection of peptides all of which comprise at least one ***T cell epitope*** and which are ***not conjugated to any other molecule.*** Accordingly, based on the teachings of Michael et al., the subject matter presently claimed by Appellants would not have been obvious to one of ordinary skill in the art. Indeed, Micheal et al. fail to provide any motivation at all to have made or used ***highly pure***, ***reproducible*** compositions of T cell epitope containing peptides in human immunotherapy, since they teach that compositions containing proteolytically cleaved allergens, which were known to be easier and less expensive to make, were sufficient for therapy.

Similar to Michael et al., Litwin et al. teach the use of compositions containing native peptic fragments obtained by digestion of chromatographic fractions enriched for ragweed allergen *Amb a* I. Thus, like Micheal et al., Litwin et al. fail to teach or suggest

a therapeutic composition made up of a ***reproducible*** selection of ***20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen*** which are ***not conjugated to any other molecule*** as claimed by Appellants.

Kuo also fails to make up for the many aforementioned deficiencies in the teachings of the above-discussed references. Kuo merely teaches whole *Fel d* I protein modified by treatment with mild base or alkali conditions to reduce IgE reactivity. As previously acknowledged by the Examiner during the personal interview conducted on December 12, 1995, Kuo et al. do not teach or suggest peptides or compositions containing peptides useful for human administration, let alone ***highly pure, reproducible T cell epitope containing peptide compositions***.

In sum, none of the cited references, either alone or in combination, provide any teaching or suggestion which would have motivated one of ordinary skill in the art to make and use a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides of which are ***not conjugated to any other molecule,*** as claimed by Appellants. Therefore, Appellants respectfully submit that claims 108, 109, 114-117, 120-123, and 128-144 are patentable over Sehon et al., J. *Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991).

D. Rejection of Claims 109, 120, and 121 Under 35 U.S.C. § 103 as Being Obvious in Light of Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991)

Claims 109, 120, and 121 which depend from claim 108 are directed to peptides comprising specific lengths of amino acid residues for use in the claimed methods. Claim 109 is directed to at least one peptide comprising 50 amino acid residues or less. Claim

120 is directed to a peptide of any one of the compositions of claims 108-109 at least about 12 amino acid residues in length. Claim 121 is directed to at least one peptide of any one of the compositions of claims 108-109 comprising at least two peptides. The claims encompass the optimal lengths of the peptides included in the therapeutic compositions for administration to humans which are capable of down regulating an antigen specific immune response. Preferred examples of the claimed peptides are shown in SEQ ID NO:1 and SEQ ID NO:2, both of which are 27 amino acid residues in length.

Thus, the compositions encompassed by claims 109, 120, and 121 provide not only the distinct advantage of being highly effective, pure and reproducible, but also, provide the distinct advantage of being an appropriate and effective length for the treatment of humans. These advantages make the claimed compositions safer and eminently more suitable for human administration than compositions containing whole or partially digested native allergens obtained from crude allergen extracts.

As described immediately above in section C, the arguments of which are reiterated here, none of the cited references, either alone or in combination, provide any teaching or suggestion which would have motivated one of ordinary skill in the art to make and use a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides of which are ***not conjugated to any other molecule***, as claimed by Appellants. Further to the arguments set forth in section C, Appellants submit that a peptide comprising 50 amino acid residues or less for use in the claimed methods are neither taught nor suggested by the cited references, either alone or in combination.

Therefore, Appellants respectfully submit that claims 109, 120, and 121 are patentable over Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4, 338, 297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991).

E. Rejection of Claims 134-137 Under 35 U.S.C. § 103 as Being Obvious in Light of Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991)

Claims 134-137 are drawn to a method of treating allergy in humans comprising administration of at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, the peptide comprising at least about 20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen, e.g., *Fel d*l, and the peptide being reproducible and not being conjugated to any other molecule, and which specify the dosage regimens of the peptide being administered. Claim 134 is directed to administering an initial treatment of three to six dosages of the composition of any one of claims 108-109 over a period of no more than 6 weeks. Claim 135, which depends from claim 134 is directed to administering an additional administration of said composition at intervals of between about three months and one year after said initial treatment. Claim 136 is directed to initial treatment comprising increasing the dosage with each subsequent additional dosage of the composition of any one of claims 108-109. Claim 137 is directed to initial treatment comprising decreasing the dosage with each subsequent additional dosage of the composition of any one of claims 108-109.

These claimed dosage amounts have been proven to be effective in the therapeutic compositions for administration to humans. Also, the claimed dosage regimens have proven to be effective in the therapeutic compositions for administration to humans. Appellants further provide working examples of appropriate and effective dosage units and dosage regimens as described in Example 1 which describes the administration of peptides to human subjects for the treatment of cat allergy (see, the specification at page 19-24.)

Therefore, the compositions encompassed by claims 134-137 provide not only the distinct advantage of being highly effective, pure and reproducible, but also, provide the distinct advantage of being administerable to humans in appropriate and effective dosage regimens. These advantages make the claimed compositions safer and eminently more suitable for human administration than compositions containing whole or partially digested native allergens obtained from crude allergen extracts.

As described above in section C, the arguments of which are reiterated here, none of the cited references, either alone or in combination, provide any teaching or suggestion which would have motivated one of ordinary skill in the art to make and use a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides of which are ***not conjugated to any other molecule***, as claimed by Appellants. Further to the arguments set forth in section C, Appellants submit that the specified dosage units and dosage regimens for use with the claimed methods are neither taught nor suggested by the cited references, either alone or in combination.

Therefore, Appellants respectfully submit that claims 134-137 are patentable over Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991).

F. Rejection of Claims 115-117 Under 35 U.S.C. § 103 as Being Obvious in Light of Sehon et al., *J. Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991)

Claims 115-117 are drawn to a method of treating allergy in humans comprising administration of at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of

amino acid residues, the peptide comprising at least about 20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen, e.g., *Fel d*I, and the peptide being reproducible and not being conjugated to any other molecule, and which specify the percent purity of the peptide contained in the claimed composition. Claim 115, which depends from any one of claims 108-109, is directed to a peptide purified to at least about 90% purity. Claim 116, which depends from claim 115, is directed to a peptide purified to at least about 95% purity. Claim 117, which depends from claim 116, is directed to a peptide purified to at least about 97% purity. Claim 118, which depends from any one of claims 103-104 and 110-113, is directed to a peptide purified to at least about 95% purity. Claim 119, which depends from claim 118, is directed to a peptide purified to at least about 97% purity.

Based on the methods taught by Appellants for synthetically producing peptides that can be purified to homogeneity (i.e., at least 90% more preferably at least 95% and even more preferably at least 97% purity), free from all other polypeptides and contaminants, the claims encompass highly purified peptides which are free from all other polypeptide contaminants and which may be used in the therapeutic compositions of the claimed invention. Therefore, the compositions encompassed by claims 115-119 provide the distinct advantage of being reproducible and purified to homogeneity. These advantages make the claimed compositions safer and eminently more suitable for human administration than compositions containing whole or partially digested native allergens obtained from crude allergen extracts.

As described above in section C, the arguments of which are reiterated here, none of the cited references, either alone or in combination, provide any teaching or suggestion which would have motivated one of ordinary skill in the art to make and use a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides of which are ***purified to at least about 90%***, as claimed by Appellants. Further to the arguments set forth in section C, Appellants submit that peptides purified to at least about

95%, and peptides purified to at least about 97% used in the claimed methods are neither taught nor suggested by the cited references, either alone or in combination.

Therefore, Appellants respectfully submit that claims 115-119 are patentable over Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991).

G. Rejection of Claims 122-123 Under 35 U.S.C. § 103 as Being Obvious in Light of Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al.,U.S. patent 4,338,297 (issued 1992) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991)

Claims 122-123 are drawn to a method of treating allergy in humans comprising administrating to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, the peptide comprising at least about 20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen, e.g., *Fel d*I, and the peptide being reproducible and not being conjugated to any other molecule, and wherein the protein allergen to be treated is selected from the protein allergens of a specific genus or is selected from a group of designated protein allergen species.

The genuses and species specified in claims 122 and 123 encompass the protein allergens amenable to the claimed methods as determined by Appellants' experimental analyses. Therefore, the compositions encompassed by claims 122-123 provide not only the distinct advantage of being highly pure and reproducible, but also, provide the distinct advantage being directed to specific protein allergens amenable to the treatment of the claimed methods. These advantages make the claimed compositions safer and eminently

more suitable for human administration than compositions containing whole or partially digested native allergens obtained from crude allergen extracts.

As described above in section C, the arguments of which are reiterated here, none of the cited references, either alone or in combination, provide any teaching or suggestion which would have motivated one of ordinary skill in the art to make and use a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides of which are ***not conjugated to any other molecule***, as claimed by Appellants. Further to the arguments set forth in section C, appellants submit that the treatment of the specific protein allergens delineated in claims 122 and 123 are neither taught nor suggested by the cited references, either alone or in combination.

Therefore, Appellants respectfully submit that claims 122-123 are patentable over Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991).

H. Rejection of Claims 138-144 Under 35 U.S.C. § 103 as Being Obvious in Light of Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991)

Claims 138-144 are drawn to a method of treating allergy in humans comprising administrating to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, the peptide comprising at least about 20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen, e.g., *Fel d*I, and the peptide being reproducible and not being conjugated to any other molecule, and wherein treatment results in a statistically significant improvement. Claim 138 is directed to a

method of treatment of any one of claims 108-109 resulting in a statistically significant improvement in symptoms caused by the human's immune response to the protein allergen. Claims 139-141 depend from claim 128. Claim 139 is directed to treatment resulting in at least about 17.5% improvement, as compared to placebo, in symptoms caused by the human's immune response to the protein allergen. Claim 140 is directed to treatment resulting in at least about 9% improvement, as compared to placebo, in nasal symptoms caused by the human's immune response to the protein allergen. Claim 141 is directed to treatment resulting in at least about 17.5% improvement, as compared to placebo, in lung symptoms caused by the human's immune response to the protein allergen. Claims 142-144 depend from claim 139. Claim 142 is directed to treatment resulting in at least about 31% improvement. Claim 144 is directed to treatment resulting in at least about 28.5% improvement.

The therapeutic treatment resulting in the percent improvement in humans which is encompassed in claims 138-144 further define the results expected utilizing the claimed invention. Appellants further provide working examples of the percent improvements calculated in Example 1 which describes the administration of peptides to human subjects for the treatment of cat allergy (see, the specification at pages 19-24.) Therefore, the peptides encompassed by claims 122-123 provide not only the distinct advantage of being highly pure and reproducible, but also, the methods of these claims quantify the improvement in symptoms in the subjects which are administered the claimed invention. These advantages make the claimed compositions safer and eminently more suitable for human administration than compositions containing whole or partially digested native allergens obtained from crude allergen extracts.

As described above in section C, the arguments of which are reiterated here, none of the cited references, either alone or in combination, provide any teaching or suggestion which would have motivated one or ordinary skill in the art to make and use a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides of

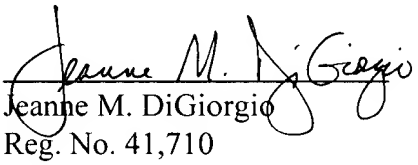
which are ***not conjugated to any other molecule***, as claimed by Appellants. Further to the arguments set forth in section C, Appellants submit that the percent improvement delineated in claims 138-144 are neither taught nor suggested by the cited references, either alone or in combination.

Therefore, Appellants respectfully submit that claims 138-144 are patentable over Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991).

IV. CONCLUSION

Appellant submits that the pending claims are patentable and it is respectfully requested that the Board reverse the final rejection of all the claims for the reasons given above.

Respectfully submitted



Jeanne M. DiGiorgio
Reg. No. 41,710
Attorney for Appellants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
(617) 227-7400

Dated: October 26, 1998

APPENDIX OF PENDING CLAIMS

108. A method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide comprising at least about 20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen, said peptide being reproducible and not being conjugated to any other molecule.

109. The method of claim 108, wherein the peptide comprises 50 amino acid residues or less.

114. The method as in any one of claims 108-109 wherein the peptide is modified by at least one amino acid substitution, addition or deletion, said peptide comprising a T cell epitope recognized by a T cell receptor specific for the protein allergen.

115. The method as in any one of claims 108-109, wherein the peptide is purified to at least about 90% purity.

116. The method of claim 115, wherein the peptide is purified to at least about 95% purity.

117. The method of claim 116, wherein the peptide is purified to at least about 97% purity.

120. The method as in any one of claims 108-109, wherein the peptide is at least about 12 amino acid residues in length.

121. The method as in any one of claims 108-109, wherein the at least one peptide comprises at least two peptides.

122. The method as in any one of claims 108-109, wherein the protein allergen is selected from the group consisting of: a protein allergen of the genus *Dermatophagoides*; a protein allergen of the genus *Felis*; a protein allergen of the

genus *Ambrosia*; a protein allergen of the genus *Lolium*; a protein allergen of the genus *Cryptomeria*; a protein allergen of the genus *Alternaria*; a protein allergen of the genus *Alder*; a protein allergen of the genus *Betula*; a protein allergen of the genus *Quercus*; a protein allergen of the genus *Olea*; a protein allergen of the genus *Artemisia*; a protein allergen of the genus *Plantago*; a protein allergen of the genus *Parietaria*; a protein allergen of the genus *Canine*; a protein allergen of the genus *Blattella*; a protein allergen of the genus *Apis*; a protein allergen of the genus *Cupressus*; a protein allergen of the genus *Juniperus*; a protein allergen of the genus *Thuya*; a protein allergen of the genus *Chamaecyparis*; a protein allergen of the genus *Periplaneta*; a protein allergen of the genus *Agropyron*; a protein allergen of the genus *Secale*; a protein allergen of the genus *Triticum*; a protein allergen of the genus *Dactylis*; a protein allergen of the genus *Festuca*; a protein allergen of the genus *Poa*; a protein allergen of the genus *Avena*; a protein allergen of the genus *Holcus*; a protein allergen of the genus *Anthoxanthum*; a protein allergen of the genus *Arrhenatherum*; a protein allergen of the genus *Agrostis*; a protein allergen of the genus *Phleum*; a protein allergen of the genus *Phalaris*; a protein allergen of the genus *Paspalum*; and a protein allergen of the genus *Sorghum*.

123. The method of claim 122, wherein the protein allergen is selected from the group consisting of: *Der p* I; *Der p* II; *Der p* III; *Der p* VII; *Der f* I; *Der f* II; *Der f* III; *Der f* VII; *Fel d* I; *Amb a* I.1; *Amb a* I.2; *Amb a* I.3; *Amb a* I.4; *Amb a* II; *Lol p* I; *Lol p* II; *Lol p* III; *Lol p* IV; *Lol p IX* (*Lol p* V or *Lol p* Ib); *Cry j* I; *Cry j* II; *Can f* I; *Can f* II; *Jun s* I; *Jun v* I; *Dac g* I; *Poa p* I; *Phl p* I; and *Sor h* I.

128. The method as in any one of claims 108-109, wherein the composition further comprises a pharmaceutically acceptable carrier.

129. The method of claim 128, wherein the pharmaceutically acceptable carrier comprises at least one excipient selected from the group consisting of sterile water, sodium phosphate, mannitol, sorbitol, sodium chloride, and any combination thereof.

130. The method as in any one of claims 108-109, wherein the composition is soluble in an aqueous solution at a physiologically acceptable pH.

131. The method as in any one of claims 108-109, wherein said administering comprises a route of administration selected from the group consisting of oral, intravenous, sublingual, transdermal, inhalation, subcutaneous and rectal.

132. The method of claim 131, wherein said administering comprises subcutaneous administration of said composition.

133. The method as in any one of claims 108-109, wherein said composition is administered without adjuvant.

134. The method as in any one of claims 108-109 comprising administering an initial treatment of three to six dosages of said composition over a period of no more than 6 weeks.

135. The method of claim 134 further comprising administering an additional administration of said composition at intervals of between about three months and one year after said initial treatment.

136. The method as in any one of claims 108-109, wherein said initial treatment comprises increasing the dosage with each subsequent additional dosage of said composition.

137. The method as in any one of claims 108-109, wherein said initial treatment comprises decreasing the dosage with each subsequent additional dosage of said composition.

138. The method as in any one of claims 108-109, wherein treatment results in a statistically significant improvement in symptoms caused by the human's immune response to the protein allergen.

139. The method of claim 128, wherein treatment results in at least about 17.5% improvement, as compared to placebo, in symptoms caused by the human's immune response to the protein allergen.

140. The method of claim 128, wherein treatment results in at least about 9% improvement, as compared to placebo, in nasal symptoms caused by the human's immune response to the protein allergen.

141. The method of claim 128, wherein treatment results in at least about 17.5% improvement, as compared to placebo, in lung symptoms caused by the human's immune response to the protein allergen.

142. The method of claim 139, wherein the treatment results in at least about 23% improvement.

143. The method of claim 139, wherein the treatment results in at least about 31% improvement.

144. The method of claim 139, wherein the treatment results in at least about 28.5 % improvement.